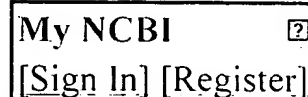




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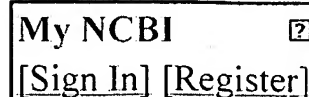
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AN      2006187607      MEDLINE
DN      PubMed ID: 16585559
TI      NF-kappaB-inducing kinase is involved in the activation of the
CD28
      responsive element through phosphorylation of c-Rel and
regulation of its
      transactivating activity.
AU      Sanchez-Valdepenas Carmen; Martin Angel G; Ramakrishnan
Parameswaran;
      Wallach David; Fresno Manuel
CS      Centro de Biologia Molecular, Consejo Superior de Investigaciones
      Cientificas, Universidad Autonoma de Madrid, Madrid, Spain.
SO      Journal of immunology (Baltimore, Md. : 1950), (2006 Apr 15)
Vol. 176, No.
      8, pp. 4666-74.
      Journal code: 2985117R. ISSN: 0022-1767.
CY      United States
DT      Journal; Article; (JOURNAL ARTICLE)
      (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA      English
FS      Abridged Index Medicus Journals; Priority Journals
EM      200605
ED      Entered STN: 5 Apr 2006
      Last Updated on STN: 17 May 2006
      Entered Medline: 16 May 2006
AB      Previous evidence suggested that NF-kappaB-inducing kinase (NIK)
might
      regulate IL-2 synthesis. However, the molecular mechanism is not
understood. In this study, we show that NIK is involved in CD3
plus CD28
      activation of IL-2 transcription. Splenic T cells from aly/aly
mice (that
      have a defective NIK protein) have a severe impairment in IL-2
and GM-CSF
```

but not TNF secretion in response to CD3/CD28. This effect takes place at the transcriptional level as overexpression of alyNIK inhibits IL-2 promoter transcription. NIK activates the CD28 responsive element (CD28RE) of the IL-2 promoter and strongly synergizes with c-Rel in this activity. We found that NIK interacts with the N-terminal domain of c-Rel, mapping this interaction to aa 771-947 of NIK. Moreover, NIK phosphorylates the c-Rel C-terminal transactivation domain (TAD) and induces Gal4-c-Rel-transactivating activity. Anti-CD28 activated Gal4-c-Rel transactivation activity, and this effect was inhibited by a NIK-defective mutant. Deletion studies mapped the region of c-Rel responsive to NIK in aa 456-540. Mutation of several serines, including Ser471, in the TAD of c-Rel abrogated the NIK-enhancing activity of its transactivating activity. Interestingly, a Jurkat mutant cell line that expresses one of the mutations of c-Rel (Ser471Asn) has a severe defect in IL-2 and CD28RE-dependent transcription in response to CD3/CD28 or to NIK. Our results support that NIK may be controlling CD28RE-dependent transcription and T cell activation by modulating c-Rel phosphorylation of the TAD. This leads to more efficient transactivation of genes which are dependent on CD28RE sites where c-Rel binds such as the IL-2 promoter.

L2 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
AN 2001370772 MEDLINE
DN PubMed ID: 11278268
TI Effects of the NIK aly mutation on NF-kappaB activation by the Epstein-Barr virus latent infection membrane protein, lymphotoxin beta receptor, and CD40.
AU Luftig M A; Cahir-McFarland E; Mosialos G; Kieff E
CS Departments of Microbiology and Molecular Genetics and Medicine, Program in Virology, Harvard Medical School, Boston, Massachusetts 02115, USA.
NC CA47006 (NCI)
SO The Journal of biological chemistry, (2001 May 4) Vol. 276, No. 18, pp.

14602-6. Electronic Publication: 2001-03-14.

Journal code: 2985121R. ISSN: 0021-9258.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LA English

FS Priority Journals

EM 200106

ED Entered STN: 2 Jul 2001

Last Updated on STN: 5 Jan 2003

Entered Medline: 28 Jun 2001

AB Homozygosity for the aly point mutation in NF-kappaB-inducing kinase (NIK)

results in alymphoplasia in mice, a phenotype similar to that of homozygosity for deletion of the lymphotoxin beta receptor

(LTbetaR). We

now find that NF-kappaB activation by Epstein-Barr virus latent membrane

protein 1 (LMP1) or by an LMP1 transmembrane domain chimera with the

LTbetaR signaling domain in human embryonic kidney 293 cells is selectively inhibited by a wild type dominant negative NIK comprised of amino acids 624-947 (DN-NIK)

and not by aly DN-NIK. In contrast, LMP1/CD40 is inhibited by both wild

type (wt) and aly DN-NIK. LMP1, an LMP1 transmembrane domain chimera with

the LTbetaR signaling domain, and LMP1/CD40 activate NF-kappaB in wt or

aly murine embryo fibroblasts. Although wt and aly NIK do not differ in

their in vitro binding to tumor necrosis factor receptor-associated factor

1, 2, 3, or 6 or in their in vivo association with tumor necrosis factor

receptor-associated factor 2 and differ marginally in their very poor

binding to IkappaB kinase beta (IKKbeta), only wt NIK is able to bind to

IKKalpha. These data are compatible with a model in which activation of

NF-kappaB by LMP1 and LTbetaR is mediated by an interaction of NIK or a

NIK-like kinase with IKKalpha that is abrogated by the aly mutation. On

the other hand, CD40 mediates NF-kappaB activation through a kinase that

interacts with a different component of the IKK complex.